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(54) Title: INCORPORATION OF LATENT ACID SOLUBILIZING AGENTS IN COATED PELLET FORMULATIONS TO OBTAIN pH INDEPENDENT RELEASE

(57) **Abstract**

This invention is directed to a composition and method for the sustained delivery of an orally administered pharmaceutical agent where said agent has a pH dependent solubility profile. A pH independent release for drugs with pH dependent solubility is accomplished through the incorporation of a latent acid member with the pharmaceutical agent in the core of the tablet or pellet formulation which maintains the microenvironmental pH within and around the tablet or pellet in the solubility pH range of the pharmaceutical agent.

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INCORPORATION OF LATENT ACID SOLUBILIZING AGENTS IN COATED PELLET FORMULATIONS TO OBTAIN pH INDEPENDENT RELEASE

BACKGROUND OF THE INVENTION

The present invention relates to the controlled in vivo release of an active drug having pH dependent solubility from pellet formulations, comprised of a solid core containing the drug, a latent acid solubilizing agent, and an outer rate controlling polymeric membrane. Because the drug has a pH dependent solubility, the pellet formulation contains one or more latent acid solubilizing agents that hydrolyze and alter the microenvironmental pH such that the drug becomes soluble even where the surrounding pH would tend to limit or inhibit drug solubility.

Several illnesses, such as hypertension and angina pectoris, require continuous and constant controlled drug release at therapeutic levels. In such instances, medications must be administered at consistent intervals, e.g. every six to eight hours, so as to maintain a therapeutically effective blood concentration of the active agent. When using medications such as diltiazem, which has a short half-life in blood of approximately three to four hours, such administration becomes even more inconvenient. Such frequent administration times render the treatment annoying to the patient and impractical to administer, particularly during the night. Furthermore, after each administration of an immediate release form of such medications, the metabolic system undergoes a succession of rapidly increasing, followed by rapidly decreasing, plasma concentrations of the pharmaceutical agent or drug. Thus, the patient being treated and the targeted organ, e.g., the cardiac system, are successively subjected to plasma drug levels above and then below the desired therapeutic level. When plasma drug levels are higher than desired there are obvious disadvantages, i.e. waste of drug, possibility of toxicity, development of drug resistance, and the like. On the other hand, when plasma levels are lower than desired the drug may be ineffective or of marginal benefit. Obviously, it would be beneficial to maintain plasma drug levels as close to the optimal therapeutic level as possible.

A drug that has pH dependent solubility usually shows a pH dependent release rate relative to the formation of its corresponding salt species. Examples of such drugs include but are not limited to verapamil, diltiazem, albuterol, propranolol, bromocriptine, chlorphenaramine, prochlorperazine, dextromethorphan, enalapril, labetalol, nicardipine, pentazocine, phenylpropanolamine, promethazine, diphenhydramine, metoclopramide, selegiline, timolol, trimethobenzamide, and quinidine, etc. These drugs contain a basic side chain moiety such that, at basic pHs, the drug is charge neutral and therefore is less soluble in aqueous systems. Indeed, such drugs are soluble only if ionized, such as when an acidic salt is formed. Therefore, pH dependent drugs, such as enumerated herein, require the continued, consistent formation of a salt of the drug so as to ensure hydrophilic solubility and thus bioavailability. Unfortunately, the digestive tract does not favor the use of the acidic salts of these drugs. The digestive tract is known to vary in pH from about 1 to 2 in the stomach to a neutral or even a basic pH in the duodenum and small and large intestines. This wide variation of pH renders the acid soluble drugs less and less soluble, and hence less bioavailable, as they traverse the digestive tract.

It has been historically problematic to achieve a controlled, sustained release of a pharmaceutical agent throughout all portions of the digestive system because of this varying pH range. One approach to solving this problem is disclosed in U.S. Patent No. 5,202,128 to Angelo M. Morella, wherein is disclosed a pharmaceutical pellet composition having a core element including at least one highly soluble active ingredient and a core coating, which is partially soluble at a highly acidic pH. The pharmaceutical composition also includes a slow release of active ingredients at the acidic pH of the stomach and additionally provides a constant, relatively faster rate of release of a pharmaceutical agent at the more alkaline pH of the intestine. This patent discloses a method and composition whereby the pellet composition is altered such that the polymers selectively included in the pellet composition have increased or decreased solubility based on the changes in pH within the biological system. However, this invention does not take into account those pharmaceutical agents which are insoluble themselves at more basic pH levels. This patent appears to conclude that all pharmaceuticals are bioavailable even under basic conditions. The

disclosed invention therefore fails to solve the problem of affording solubility to those pharmaceutical agents which have pH dependent solubility.

Additional attempts at pH independent release rates of drugs having a pH dependent solubility profile have been disclosed by a variety of approaches such as the addition of an organic acid to a pellet formulation comprising a core made up of layers of the active agent and/or a salt thereof, and a polymeric material whereby the environment around the pellet becomes selectively acidic on a time release basis as disclosed in U.S. Patents 4,721,619; 4,826,688 and 4,863,742. Illustrative of organic acids that can be employed include acids such as adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and mixtures or combinations thereof. Disadvantages to this approach are stability of acid labile drugs while in the solid state in the pellet, stomach discomfort caused by the additional acid, and depletion of the added acid prior to complete dissolution and release of the drug.

An additional approach, which does not utilize organic acids, makes use of surfactants or wetting agents in the solid supports used for administration of these pharmaceutical agents, to increase solubility of the hydrophobic drug into the hydrophilic biological environment as disclosed in U.S. Patents 5,288,505 and 5,529,791. The surfactants or wetting agents include fatty acid esters of saccharose (commercialized under the trade names of SUCROESTERS and CRODESTERS), generically xylose esters or xylites, polyoxyethylenic glycerides, esters of fatty acids and polyoxyethylene sorbitan fatty acid esters, and polyglycides-glycerides as disclosed in U.S. Patent No. 5,288,505. However, the addition of such acids and/or surfactants may compromise the stability of certain drugs and/or may cause processing problems due to the corrosive nature of the acids used. It would therefore be useful to achieve the pH independent bioavailability of a drug having a pH dependent solubility profile. It would furthermore be useful to achieve these goals without alteration of the ambient pH, or through the addition of surfactants to facilitate the assimilation of the hydrophobic drug in a hydrophilic biological environment.

OBJECTS OF THE INVENTION

It is therefore an object of this invention to provide for the controlled release of active pharmaceutical agents independent of ambient pH even though said agents have pH dependent solubilities.

It is another object of this invention to provide a drug delivery composition which avoids undesirable acid-drug interactions yet promotes the solvation of an acid soluble drug in an increasingly basic environment.

It is a further object of this invention to provide a drug delivery composition which allows for solvation of an active drug which is soluble in an acid environment but less soluble in a basic environment even though the ambient environmental pH progresses from acidic to basic pH.

It is an additional object of this invention to provide a formulation whereby an acidic microenvironmental pH is maintained, facilitating the pH dependent solubility of the desired pharmaceutical agent, without necessitating an ambient alteration of pH.

The above objects and others, which will become apparent in view of the following discussion and examples, are achieved by means of an extended release form of a pharmaceutically acceptable system which comprises a pellet formulation wherein the core of said pellet contains the drug and a latent acid which hydrolyzes under mildly basic conditions creating an acidic microenvironment whereby the solvation of the active drug is achieved. Additionally, the pellet is coated with an outer rate controlling polymeric membrane.

From the following summary it will also become apparent that the invention provides distinct advantages in compounding compositions of drugs having pH dependent solubilities. The addition of a latent acid to the solid formulation will not change the overall pH and will therefore promote stability over similar formulations containing acids that might affect the stability of the acid labile drugs. Solid formulations not containing acids will prevent processing difficulties, such as corrosion, that might otherwise arise. Also, latent acids will protect against interaction between the acid, drug and other constituents of the composition such as binders, diluents, and lubricants.

SUMMARY OF THE INVENTION

Accordingly, this invention provides a coated pellet formulation which accomplishes the previously set forth goal of providing controlled release of an active drug wherein the release profile is pH independent even though the drug solubility profile is pH dependent. This goal is accomplished through the incorporation of a latent acid, such as glucono delta-lactone or similar lactone, lactam, amide or ester, into the pellet or tablet formulation along with the drug. The selection of the latent acid portion of the formulation is dictated to some degree by the specific solubility characteristics of the pharmaceutical agent to be delivered and where along the digestive tract the drug is to be delivered. An ester based latent acid species would, for example, provide a better microenvironment for enhancing the delivery of a specific class of drug targeted for the lower GI tract where the pH is more basic, whereas the lactone based type of latent acid would be better suited to a class of drug which is to be delivered in the upper GI tract where the pH is more neutral. The latent acid can be selected and formulated to hydrolyze at a desired pH. The latent acid used may be, for example, a member such as an amide, ester, anhydride, lactame and lactone of an organic acid. Each form of latent acid presents a range of pH within which it will undergo hydrolysis. Upon hydrolysis the latent acid acidifies the microenvironment within and immediately surrounding the pellet or tablet. The microenvironmental acidification is sufficient to facilitate the solvation and release of the active drug even where the macroenvironmental surrounding pH is prejudicial to the drug's solubility. The prudent selection of the latent acid included in the formulation specifies the pH at which the latent acid will hydrolyze and at which the delivery of the active drug will commence. A polymeric coating is also applied to the pellet to control the drug release rate by facilitating hydrolysis of the latent acid at the appropriate macroenvironmental pH and solubilization of the drug. The coating material is both water and drug permeable. In this manner, the coating allows the migration of water into the tablet and the movement of latent acid/hydrolyzed acid and active drug out of the tablet. The coating may also be selectively water soluble. Water solubility of the coating is useful, for example, where increased permeability is desired or where other

requirements of the active drug so dictate. Selective and variable water solubility of the coating is predetermined by the chemical composition of the coating material. Increasing the thickness of the coating is one way that the coating solubility is altered. Thickness and composition of the coating will influence the rate of drug release.

Glucono delta-lactone, one specific example of a type of latent acid, offers various advantages over previously reported organic acids. Glucono delta-lactone is a neutral molecule since it is a lactone of gluconic acid possessing no acidic functional groups. In solid state, this molecule does not have an adverse affect on drug stability, even for drugs that are acid labile. Likewise, because this formulation does not have a free acid grouping, the latent acid moiety does not interact with other components used in the formulation.

Specifically, in vivo, at an appropriate pH, glucono delta-lactone will be hydrolyzed into gluconic acid, which acidifies the microenvironment within the pellets, thereby solubilizing the drug, irrespective of the surrounding pH. From a chemical stability standpoint, the formulation contains a lactone, which is pH neutral, and does not change the pH of the formulation in solid state. However, the lactone behaves as a latent acid since, in the presence of an aqueous environment and at a more basic pH, it hydrolyzes into gluconic acid.

The kinetics of conversion of glucono delta-lactone to gluconic acid provides an added advantage to this approach. Initially, upon administration when the formulation is in the stomach, the drug solubility is high in the acidic gastric macroenvironment. By the time the formulation undergoes gastrointestinal transit and the pH slowly becomes more basic, the glucono delta-lactone is hydrolyzed into gluconic acid. Through this hydrolysis, this latent acid form is converted into a free acid. The free acid is able to discharge its protons causing an acidification of the microenvironment. This mechanism allows the latent acid portion of the formulation to maintain the acidic microenvironmental pH within the pellet. Thus, by the time the formulation reaches the higher physiological pH of the intestine, which is inimical to drug solubility of acid dependent soluble drugs, the lowering of the

microenvironmental pH is achieved by hydrolysis of the latent acid, thereby overcoming the pH dependent drug solubility problem.

The maintenance of the pH within the solubility range of the drug in the microenvironment of the pellet formulation facilitates the absorption of the active drug. This ability to alter the microenvironmental pH within and in the immediate environs of the pellet becomes increasingly important as the pellet traverses the alimentary canal from the stomach to the lower GI. The pH changes significantly between the stomach, where the pH is very acidic, to the lower GI, where the pH is more basic, e.g., in the region of pH 7 or even higher. For sustained drug delivery along the lower alimentary tract it is important to deliver an active agent, which is only soluble under acidic pH, in a bioavailable form. A formulation which contains a latent acid facilitates this delivery because, under conditions which are more pH basic, the latent acid is hydrolyzed into the acid causing the microenvironmental pH of the pellet to become acidic. Thus, when the pellet formulation of the present invention reaches the higher physiological pH of the intestinal tract, the desired microenvironmental acidic pH of the pellet is maintained and the drug is made bioavailable in soluble form.

PREFERRED EMBODIMENTS

The following definitions will be helpful in defining terms used in this invention and will avoid repetitive explanation of terminology.

The term "microenvironment," "microenvironmental," and the like shall mean the environment within and immediately surrounding the pellet or tablet. The environment within and immediately surrounding the pellet or tablet shall mean the inner portion of the pellet or tablet and the outer shell layer, including a limited area surrounding the pellet or tablet.

The term "permeable polymer" and the like shall mean a polymer that is permeable to water, the latent acid, the hydrolyzed acid, and the active drug. This term includes bi-directional permeation such that simultaneous in-flux and out-flow of any or all of these molecules occurs. The coating allows the movement of water, the latent acid, the hydrolyzed acid and the active drug out of the pellet or tablet.

Likewise, the permeability of the coating allows for transfer of water into the core to cause the hydrolysis of the latent acid. Importantly, the core is equally permeable to the latent acid and to the hydrolyzed acid. This permeability is a property of the coating. Although the permeability of the coating can be altered because of partial water solubility of the coating, the coating has the required permeability even where the coating is insoluble.

The latent acid may be any composition which will adjust the microenvironmental pH to facilitate solvation of the active drug. The term "latent acid" preferably means any lactone, anhydride, amide, lactam, ester, and the like of any organic acid that hydrolyzes into an organic acid at desired rate.

The terms "drug," "active agent," "pharmaceutical," and the like shall mean any drug which is a base (in its galenical form or as its pharmaceutically acceptable salt), displaying pH dependent solubility (with higher solubility under acidic conditions and lower solubility under basic conditions). Such drugs include, but are not limited to, verapamil, diltiazem, quinidine, propranolol, bromocriptine, chlorphenaramine, prochlorperazine, dextromethorphan, enalapril, labetalol, nicardipine, pentazocine, phenylpropanolamine, promethazine, diphenhydramine, metoclopramide, selegiline, timolol, trimethobenzamide, and albuterol, in their galenical form or as their pharmaceutically acceptable salts (such as hydrochloride, sulfate, hydrobromide and phosphate salts).

Various conventional tableting or pelleting agents such as binders, fillers, lubricants and the like may be included in the formation of the tablets or pellets containing the drug and latent acid. While such ingredients promote the functionality of the invention, they, by themselves, are not novel ingredients.

The term "binder" refers to an agent that contributes to the cohesiveness of the tablet or pellet and can be any ingredient conventionally used as such. Examples of suitable binders are polymers such as povidone, starch, natural gums, hydroxypropyl methyl cellulose or sucrose.

The term "diluent" means an inert ingredient utilized as a carrier or as a provider of bulk to the tablet or pellet. Exemplary of a suitable carrier is microcrystalline cellulose, due to its ability to be extruded and spheronised. The

inclusion of a diluent facilitates the fabrication of the tablet or pellet. Any other suitable diluents could be used provided they are functional in the extrusion and spheronization of the tablet or pellet.

The term "lubricant" refers to any ingredient that enables the tablet or pellet to be mechanically formed without adhering to the pelleting or coating machinery. Also, the lubricant shall mean additives that reduce pellet to pellet or tablet to tablet adherence concerns. Examples of lubricants are talc or magnesium stearate.

Essential to the formation of the core or body of the tablets or pellets is the drug and latent acid. The drug to latent acid ratios may vary depending upon the specific pH dependency or solubility characteristics of the drug, the strength of the latent acid, and the like. Generally, the weight ratio of the drug to latent acid may vary between about 1:99 to 50:1 with ratios of about 1:10 to 5:1 being preferred. Optimal ratios of drug to latent acid are about 2:1.

The drug/latent acid will comprise between about 5 to 90% by weight of the uncoated tablet or pellet. Preferably the inert ingredients such as binders, diluents, lubricants and the like will be present in amounts of between about 10 to 95% by weight. In other words, the drug/latent acid will comprise between about 5 to 90% by weight of the tablet or pellet with amounts of between about 60 to 90% being preferred for high dose drugs, between 5 to 20% being preferred for low dose drugs, and 20 to 60% being preferred for medium dose drugs. The remainder of the composition will be made up of the above mentioned inert ingredients.

The core tablets or pellets are prepared by conventional techniques. For example, the dry ingredients can be combined in a blender followed by the addition of an appropriate amount of water or other suitable binding agent to form a wet mass which is then extruded through a screen into plastic extrudates which are then processed into spherical tablets or pellets using a spheroniser. If certain ingredients, such as povidone, are to be added as a solution, the dry ingredients are first blended and then the additional ingredients are added as an aqueous solution and extruded by using wet extrusion followed by spheronisation and other techniques known in the art. The tablets or pellets are then dried at elevated temperatures preparatory to being coated by a time release polymeric coating.

The polymeric coating is applied to the tablets or pellets in a single coating or multiplicity of coatings using conventional coating techniques. The coating is a polymer or mixture of polymers having varying degrees of hydrophilicity and/or hydrophobicity. It is the permeability profile of the coating that enables the entry of water into the tablet or pellet. Likewise, the permeability profile of the coating facilitates the outward movement of both the acid and active drug into the macroenvironment. At the higher pH environment of the intestinal tract this influx of water at a basic pH causes the hydrolysis of the latent acid to its acid form, decreasing the microenvironmental pH and thereby solubilizing the drug that would otherwise be insoluble in that environment. The solubilized drug is then released from the tablet or pellet through the coating into the macroenvironment of the digestive tract for absorption. Hence, it is the coating that controls the drug release rate secondary to the macroenvironmental pH controlling the hydrolysis of the latent acid that enables the solubility of the drug for release.

Polymeric coatings of limited water solubility having increased solubility at higher pH ranges, as encountered in the small and large intestines, which are suitable for the pH independent release of drugs, are known in the art and are adequately disclosed in U.S. Patents 5,202,128; 5,330,766 and 5,378,474. No claim is made as to the discovery of any novel polymeric coatings, but rather claim is made to the discovery that drugs, having acid dependent solubilities, may be rendered soluble independent of the macroenvironmental pH, by means of the incorporation of a latent acid into the tablet or pellet core which is then coated with a polymeric coating of selectable permeation, water solubility and which is preferably increasingly permeable at increasing pH ranges.

An equally viable mechanism of action of the present invention proceeds along similar pathways except that the delivery of the drug is not dependent upon the solvation of the drug within the confining of the tablet or pellet. It is within the scope of this invention for the drug to exit the tablet or pellet into the immediate exterior microenvironment, where, if the pH is acidic, the drug will be easily dissolved and absorbed. However, as the pH rises, the latent acid will be hydrolyzed and cause a lowering of the microenvironmental pH in the surrounding tablet or

pellet microenvironment. This will in turn facilitate the solvation of the acid soluble drug with resultant increase in its release activity.

For example, the polymers utilized may be hydrophobic polymers such as ethyl cellulose, with or without a hydrophilic polymer, such as hydroxypropyl methyl cellulose, along with a plasticizer such as polyethylene glycol, polysorbate 80, glycerol, and the like. Illustrative of such polymeric coatings are those marketed under the trade name SURELEASE and OPADRY (manufactured by Colorcon). SURELEASE is a formulated hydrophobic polymer suspension containing ethyl cellulose and a plasticizer. OPADRY is a hydrophilic powder formulation containing hydyoxypropyl methyl cellulose and a plasticizer.

Aqueous coating suspensions of the above mentioned ethyl cellulose or combinations of ethyl cellulose and hydroxypropyl methyl cellulose, mixed in different proportions, have been successfully employed in making coated tablets or pellets. These coating compositions can range from 100% ethyl cellulose to a mixture containing ethyl cellulose and hydroxy propyl cellulose in a variety of weight ratios such as 95:5, 90:10, 80:20, 75:25, 70:30, 60:40 or 50:50. This combination of a hydrophilic and hydrophobic polymers allows controlled designation of the water solubility of the tablet or pellet coating. The coatings can be formed from any combination of water soluble and water insoluble components as long as the desired level of water solubility and coating film permeability is accomplished.

Use of ethyl cellulose and hydroxy propyl methylcellulose is not restricted to the above mentioned products. For example, an ethyl cellulose manufactured by FMC Corporation under the trade name AQUACOAT may also be employed.

Other polymeric coatings may be utilized in the place of cellulosic polymers. For example, acrylic resins such as those sold by Creanova Inc. under the trade names EUDRAGITS RS, RL, and NE may also be used in the present invention, where these polymeric coatings are representative of coatings with hydrophobic, hydrophillic and neutral characteristics known in the art. These acrylic resins may be combined in appropriate proportions to achieve the desired release rates and coating solubility. Plasticizers such as triethyl citrate, tributyl citrate, acetyl tributyl

citrate, and dibutyl sebacate may be added as a component to acrylic coatings as may a processing aid such as talc. Again reference is made to U.S. Patents 5,202,128; 5,330,766 and 5,378,474 as representative of coatings that may be used to coat the acid labile drugs and latent acids which form the basic ingredients of the tablets or pellets of the present invention.

The tablets or pellets can be formulated such that each contains an effective unit dosage of the acid soluble drug or, in the alternative, a multiplicity of tablets or pellets may be required to achieve a unit dosage form. The drug/latent acid ratio within the tablet or pellet and coating of the tablet or pellet may be different for each type of tablet or pellet in a dosage form if comprised of more than one type of tablet or pellet.

EXAMPLES

Specific examples showing the use of glucono-δ-lactone as the latent acid and the demonstration of pH independent release rates for drugs with pH dependent solubilities are described below.

EXAMPLE 1

A representative tablet or pellet formulation having the following composition was prepared as shown:

Ingredients	% w/w	mg/dose
Verapamil HCl	58	240
Glucono-δ-Lactone	29	120
[1]Avicel PH101	11	45.5
[2]Povidone K-29/32	2	8.3

[1]microcrystalline cellulose
[2]polyvinylpyrrolidone

All the ingredients, except Povidone, were blended together as powders in the ratio shown above, and then transferred into a Hobart-type blender. The powder mixture was granulated by adding additional water to a solution of Povidone (33%

w/w) until the wet mass, when passed through 0.6 mm screen of the extruder, yielded plastic extrudates. The extruder used was Nica-Extruder E-140, made by Niro-Fielder. The extrudates were then processed into spherical pellets using Nica-Spheroniser S-450 (Niro-Fielder). The pellets were dried at 50°C for 16 hours. The particle fractions between 20 mesh and 35 mesh were separated using sieves and then used as the pellets to be coated.

Coating was done in a Niro-Aeromatic MP-1 fluid bed coater with a Wurster insert. The coating suspension of ethyl cellulose (Surelease E-7-19010) was diluted with water to give a 10% solids content and then sprayed onto the core pellets until 10% weight gain was achieved. The pellets were dried at 50°C for 20 hours. This coating is water insoluble, yet has the required qualities of permeation to water, the active drug, and the acid. This example shows how a coating that is water insoluble yet permeable, gives the desired pH independent solubility of the active drug. Of course, a partially water soluble coating that is permeable, as in example 2, provides equally beneficial results.

The release rates of drug from the coated pellets were obtained using USP Paddle Apparatus No. 2, in dissolution media at both pH 1.2 and pH 7.5. The dissolution rates were found to be pH independent as shown:

Time	**% Release, Mean ± SD (n=6) at**	
(Hours)	**pH 1.2**	**pH 7.5**
0.5	10.6±1.1	9.3±1.5
1	18.5±1.8	19.6±1.9
2	30.6±2.5	32.3±2.4
4	46.4±2.9	47.2±2.6
6	57.9±3.4	57.2±2.8
8	65.8±3.4	64.0±2.7
12	76.0±3.2	72.8±2.4
16	82.4±2.9	78.3±2.5
20	86.6±2.5	82.8±2.3
24	87.7±2.4	84.1±2.5

The solubility of verapamil at pH 1.2 is greater than 80 mg/mL, but it drops to 0.44 mg/mL at pH 7.3. This example thus demonstrates the pH independent delivery of a drug with a pH dependent solubility profile, at both acidic and neutral pH's, where the pellet is formulated with a 2:1 drug to latent acid ratio.

EXAMPLE 2

A second representative formulation of pellets having the following composition was prepared as shown:

Ingredients	% w/w	mg/dose
Diltiazem HCl	50	240
Glucono-δ-Lactone	25	120
Avicel PH101	25	120

All ingredients were powders and were blended together in the ratio shown above, and then transferred into a Hobart-type blender. The powder mixture was granulated by adding water until the wet mass, being passed through a 0.8 mm screen of the extruder, yielded plastic extrudates. The extruder used was Nica-Extruder E-140, made by Niro-Fielder. The extrudates were then processed into spherical pellets using Nica-Spheroniser S-450 (Niro-Fielder). The pellets were dried at 50°C for 20 hours. The particle fractions between 14 mesh and 30 mesh were separated using sieves and then used as the pellets to be coated.

Coating was done in a Niro-Aeromatic Strea-1 fluid bed coater with a Wurster insert. The coating suspension of ethyl cellulose (Surelease E-7-19010) was added to hydroxy propyl methylcellulose (Opadry YS-1-7006), and then dissolved in water to get a final coating suspension containing Surelease and Opadry in the ratio of 95:5 (based on solids weight) and having a total solids content of 10%. This solution mixture was then sprayed onto the core pellets until 12% weight gain was achieved. The pellets were dried at 40°C for 20 hours.

The release rates of drug from the coated pellets were obtained using USP Paddle Apparatus No. 2, in dissolution media at correspondingly pH 1.2 and pH 7.5. The dissolution rates were found to be independent of global pH as shown:

Time	% Release, Mean ± SD (n=6) at	
(Hours)	pH 1.2	pH 7.5
0.5	15.4±2.9	14.6±2.2
1	30.1±2.4	23.8±3.1
2	50.0±3.3	55.4±3.0
4	71.1±2.3	75.9±2.4
6	78.5±3.0	82.3±3.7
8	85.7±1.9	88.7±0.4
11	90.1±1.4	90.8±0.6

CONCLUSION

These examples demonstrate the ability of the present invention to deliver, independent of pH, a drug with a solubility profile that is pH sensitive. The functionality to deliver drugs, independent of pH, is particularly advantageous where the drug is to be delivered into an environment where the pH would adversely affect the efficacy and/or solubility of the drug.

It is particularly noteworthy that the latent acid is neutral in the solid state within the tablet or pellet and therefore does not change the overall pH nor adversely affect the stability of the drug in that state. However, when the macroenvironment in the alimentary canal changes from acidic to neutral or slightly basic, due to gastrointestinal transit, the pH slowly increases. Concurrently, the latent acid is converted to its acid form by hydrolysis thereby decreasing the microenvironmental pH within and immediately surrounding the tablet or pellet and causing the drug to be solubilized, thereby overcoming the pH dependent solubility problem. Although the examples have been directed to the use of a specific type of latent acid, a cyclic lactone, other types of latent acids may be used with equal efficacy. Other latent acids which are included in the

scope of this invention include esters, amines, amides anhydrides and lactames. The salient feature of each selected latent acid is the characteristic of neutrality in the solid state but acidity when hydrolyzed at a desired pH.

Accordingly, these examples demonstrate how the incorporation of a latent acid member into the formulation of a tablet or pellet allows for the delivery of a drug, which has a pH dependent solubility profile, into an adverse macroenvironment at a delivery rate which is independent of the pH of that environment.

Although the examples demonstrate preferred embodiments of this invention, it is to be understood that the invention is limited only by the following claims and their functional equivalents.

CLAIMS

What is claimed is:

1. A composition for the pH independent administration of active pharmaceutical agents having pH dependent solubilities comprising a solid pellet core containing an intimate admixture of a pharmaceutical agent of pH dependent solubility and a latent acid member that hydrolyzes into an organic acid in an aqueous environment at the ambient pH normally found in the duodenal and intestinal portions of the alimentary canal, said pellet being coated by a permeable polymeric coating.

2. The composition according to Claim 1 wherein the latent acid is a member selected from the group consisting of lactones, anhydrides, lactams and esters.

3. The composition according to Claim 2 wherein the weight ratio of pharmaceutical agent to latent acid is between about 1:99 to 50:1.

4. The composition according to claim 1 wherein the pharmaceutical agent is soluble at acid pH.

5. The composition according to Claim 3 wherein said pharmaceutical agent is selected from the group comprising: albuterol, verapamil, diltiazem, propranolol, bromocriptine, chlorphenaramine, prochlorperazine, dextromethorphan, enalapril, labetalol, nicardipine, pentazocine, phenylpropanolamine, promethazine, diphenhydramine, metoclopramide, selegiline, timolol, trimethobenzamide, quinidine and pharmaceutically acceptable salts thereof.

6. The composition according to Claim 3 wherein the latent acid is a lactone of an organic acid.

7. The composition according to Claim 6 wherein the lactone is glucono-δ-lactone.

8. The composition according to Claim 5 wherein said pharmaceutical agent is verapamil or a pharmaceutically acceptable salt thereof.

9. The composition according to Claim 5 wherein said pharmaceutical agent is diltiazem or a pharmaceutically acceptable salt thereof.

10. The composition according to Claim 5 wherein said pharmaceutical agent is quinidine or a pharmaceutically acceptable salt thereof.

11. The composition according to Claim 5 wherein said pharmaceutical agent is propanolol or a pharmaceutically acceptable salt thereof.

12. The composition according to Claim 5 wherein said pharmaceutical agent is albuterol or a pharmaceutically acceptable salt thereof.

13. The composition according to Claim 5 wherein said pharmaceutical agent is bromocriptine or a pharmaceutically acceptable salt thereof.

14. The composition according to Claim 5 wherein said pharmaceutical agent is chlorphenaramine or a pharmaceutically acceptable salt thereof.

15. The composition according to Claim 5 wherein said pharmaceutical agent is prochlorperazine or a pharmaceutically acceptable salt thereof.

16. The composition according to Claim 5 wherein said pharmaceutical agent is dextromethorphan or a pharmaceutically acceptable salt thereof.

17. The composition according to Claim 5 wherein said pharmaceutical agent is enalapril or a pharmaceutically acceptable salt thereof.

18. The composition according to Claim 5 wherein said pharmaceutical agent is labetalol or a pharmaceutically acceptable salt thereof.

19. The composition according to Claim 5 wherein said pharmaceutical agent is nicardipine or a pharmaceutically acceptable salt thereof.

20. The composition according to Claim 5 wherein said pharmaceutical agent is pentazocine or a pharmaceutically acceptable salt thereof.

21. The composition according to Claim 5 wherein said pharmaceutical agent is phenylpropanolamine or a pharmaceutically acceptable salt thereof.

22. The composition according to Claim 5 wherein said pharmaceutical agent is promethazine or a pharmaceutically acceptable salt thereof.

23. The composition according to Claim 5 wherein said pharmaceutical agent is diphenhydramine or a pharmaceutically acceptable salt thereof.

24. The composition according to Claim 5 wherein said pharmaceutical agent is metoclopramide or a pharmaceutically acceptable salt thereof.

25. The composition according to Claim 5 wherein said pharmaceutical agent is selegiline or a pharmaceutically acceptable salt thereof.

26. The composition according to Claim 5 wherein said pharmaceutical agent is timolol or a pharmaceutically acceptable salt thereof.

27. The composition according to Claim 5 wherein said pharmaceutical agent is trimethobenzamide or a pharmaceutically acceptable salt thereof.

28. The composition according to claim 1 wherein said polymeric coating is at least partially water soluble.

29. The composition according to claim 1 wherein the polymeric coating is water insoluble.

30. A method for the pH independent administration of an active pharmaceutical agent having pH dependent solubilities comprising orally administering an effective amount of said active pharmaceutical agent in the form of a solid pellet core containing an intimate admixture of said pharmaceutical agent and a latent acid member that hydrolyzes into an organic acid in an aqueous environment at the ambient pH normally found in the duodenal and intestinal portions of the alimentary canal, said pellet being coated by a permeable polymeric coating;

said administration of said pharmaceutical agent being continuous throughout the alimentary canal in that said pharmaceutical agent is naturally soluble in the acidic environment of the stomach and passes through said polymeric coating and, as the pellet enters the more basic regions of the alimentary canal where the pharmaceutical agent would not be soluble, the pharmaceutical agent continues to be solubilized by means of the hydrolysis of the latent acid creating an acidic microenvironment of said pellet.

31. The method according to Claim 30 wherein the latent acid is a member selected from the group consisting of lactones, anhydrides, lactams and esters.

32. The method according to Claim 31 wherein the weight ratio of pharmaceutical agent to latent acid is between about 1:99 to 50:1.

33. The method according to Claim 30 wherein said pharmaceutical agent is selected from the group comprising: albuterol, verapamil, diltiazem, propranolol, bromocriptine, chlorphenaramine, prochlorperazine, dextromethorphan, enalapril, labetalol, nicardipine, pentazocine, phenylpropanolamine, promethazine, diphenhydramine, metoclopramide, selegiline, timolol, trimethobenzamide, quinidine and pharmaceutically acceptable salts thereof.

34. The method according to Claim 31 wherein the latent acid is a lactone of an organic acid.

35. The method according to Claim 34 wherein the lactone is glucono-δ-lactone.

36. The method according to Claim 33 wherein said pharmaceutical agent is verapamil or a pharmaceutically acceptable salt thereof.

37. The method according to Claim 33 wherein said pharmaceutical agent is diltiazem or a pharmaceutically acceptable salt thereof.

38. The method according to Claim 33 wherein said pharmaceutical agent is quinidine or a pharmaceutically acceptable salt thereof.

39. The method according to Claim 33 wherein said pharmaceutical agent is propanolol or a pharmaceutically acceptable salt thereof.

40. The method according to Claim 33 wherein said pharmaceutical agent is albuterol or a pharmaceutically acceptable salt thereof.

41. The method according to Claim 33 wherein said pharmaceutical agent is bromocriptine or a pharmaceutically acceptable salt thereof.

42. The method according to Claim 33 wherein said pharmaceutical agent is chlorphenaramine or a pharmaceutically acceptable salt thereof.

43. The method according to Claim 33 wherein said pharmaceutical agent is prochlorperazine or a pharmaceutically acceptable salt thereof.

44. The method according to Claim 33 wherein said pharmaceutical agent is dextromethorphan or a pharmaceutically acceptable salt thereof.

45. The method according to Claim 33 wherein said pharmaceutical agent is enalapril or a pharmaceutically acceptable salt thereof.

46. The method according to Claim 33 wherein said pharmaceutical agent is labetalol or a pharmaceutically acceptable salt thereof.

47. The method according to Claim 33 wherein said pharmaceutical agent is nicardipine or a pharmaceutically acceptable salt thereof.

48. The method according to Claim 33 wherein said pharmaceutical agent is pentazocine or a pharmaceutically acceptable salt thereof.

49. The method according to Claim 33 wherein said pharmaceutical agent is phenylpropanolamine or a pharmaceutically acceptable salt thereof.

50. The method according to Claim 33 wherein said pharmaceutical agent is promethazine or a pharmaceutically acceptable salt thereof.

51. The method according to Claim 33 wherein said pharmaceutical agent is diphenhydramine or a pharmaceutically acceptable salt thereof.

52. The method according to Claim 33 wherein said pharmaceutical agent is metoclopramide or a pharmaceutically acceptable salt thereof.

53. The method according to Claim 33 wherein said pharmaceutical agent is selegiline or a pharmaceutically acceptable salt thereof.

54. The method according to Claim 33 wherein said pharmaceutical agent is timolol or a pharmaceutically acceptable salt thereof.

55. The method according to Claim 33 wherein said pharmaceutical agent is trimethobenzamide or a pharmaceutically acceptable salt thereof.

56. The method according to Claim 30 wherein said polymeric coating is at least partially water soluble.

57. The method according to Claim 30 wherein said polymeric coating is water insoluble.

58. The method according to claim 30 wherein the pharmaceutical agent is soluble in acid pH.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/17120

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/16, 9/50

US CL :424/490

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/490

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,202,128 A (MORELLA et al) 13 April 1993, col. 23, lines 33-40, col. 15, line 27, col.9, lines 59-64, col. 10, lines 4-36, col. 9, lines 4-38.	1-58

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 JANUARY 1999	Date of mailing of the international search report 03 FEB 1999
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